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# Canagliflozin and Stroke in Type 2 Diabetes Mellitus

## Results From the Randomized CANVAS Program Trials

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**Background and Purpose**—This study reports the detailed effects of canagliflozin on stroke, stroke subtypes, and vascular outcomes in participants with and without cerebrovascular disease (stroke or transient ischemic attack) at baseline from the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program.

**Methods**—The CANVAS Program, comprising 2 similarly designed and conducted clinical trials, randomly assigned 10 142 participants with type 2 diabetes mellitus and high cardiovascular risk to canagliflozin or placebo. Its primary outcome was a composite of major adverse cardiovascular events. The main outcome of interest for this report was fatal or nonfatal stroke. Additional exploratory outcomes were stroke subtypes and other vascular outcomes defined according to standard criteria.

**Results**—There were 1958 (19%) participants with prior stroke or transient ischemic attack at baseline. These individuals were older, more frequently women, and had higher rates of heart failure, atrial fibrillation, and microvascular disease (all  $P < 0.001$ ) compared with those without such a history. There were 309 participants with stroke events during follow-up (123 had prior stroke or transient ischemic attack at baseline and 186 did not), at a rate of 7.93/1000 patient-years among those assigned canagliflozin and 9.62/1000 patient-years among placebo (hazard ratio, 0.87; 95% CI, 0.69–1.09). Analysis of stroke subtypes found no effect on ischemic stroke ( $n = 253$ , hazard ratio, 0.95; 95% CI, 0.74–1.22), a significant reduction for hemorrhagic stroke ( $n = 30$ , hazard ratio, 0.43; 95% CI, 0.20–0.89) and no effect on undetermined stroke ( $n = 29$ , hazard ratio, 1.04; 95% CI, 0.48–2.22). Effects on other cardiovascular outcomes were comparable among participants with and without stroke or transient ischemic attack at baseline.

**Conclusions**—There were too few events in the CANVAS Program to separately define the effects of canagliflozin on stroke, but benefit is more likely than harm. The observed possible protective effect for hemorrhagic stroke was based on small numbers but warrants further investigation.

**Clinical Trial Registration**—URL: <https://www.clinicaltrials.gov>. Unique identifiers: NCT01032629 and NCT01989754. (*Stroke*. 2019;50:396-404. DOI: 10.1161/STROKEAHA.118.023009.)

**Key Words:** canagliflozin ■ cardiovascular diseases ■ diabetes mellitus, type 2 ■ ischemic attack, transient ■ stroke

The prevalence of type 2 diabetes mellitus has doubled over the past 3 decades and is likely to affect a half a billion people in the next 3 decades.<sup>1</sup> Given that new medications for diabetes mellitus could potentially be given to some tens of

millions of people, it is vital that these medications are safe, and in particular, not associated with an increased vascular risk.<sup>2,3</sup> The sodium glucose co-transporter 2 (SGLT2) inhibitors have recently emerged as important new treatments for

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A complete list of investigators in the CANVAS Program is provided in the [online-only Data Supplement](#).

The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.023009>.

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diabetes mellitus. The mechanism of action, by reducing the reuptake of glucose in the kidney, lowers blood glucose, with other favorable effects on biomarkers, particularly weight loss.<sup>4</sup> Evidence of the effect of SGLT2 inhibitors on vascular events has come from 2 trial programs, the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) testing empagliflozin<sup>5</sup> and the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program trials testing canagliflozin.<sup>6</sup> In the EMPA-REG OUTCOME study, there was a nonsignificant increase in the risk of stroke (hazard ratio [HR], 1.18; 95% CI, 0.89–1.56), and in the CANVAS Program, there was a nonsignificant decrease in the risk of stroke (HR, 0.87; 95% CI, 0.69–1.09). Extensive subsidiary analyses of EMPA-REG OUTCOME have not identified any adverse effect of empagliflozin that might have caused an increase in stroke risk.<sup>7</sup> Given that type 2 diabetes mellitus is associated with an approximate doubling in the risk of stroke compared with people without diabetes mellitus,<sup>8</sup> it is important to understand more about the effects of these drugs on stroke and whether those with established cerebrovascular disease have any additional risks or benefits compared with those without. The aim of this study was to explore the detailed effects of canagliflozin on stroke, stroke subtypes, and other vascular outcomes among CANVAS Program participants and to analyze whether these effects differed for those with and without a history of cerebrovascular disease (stroke or transient ischemic attack [TIA]) at baseline.

## Methods

### Program Design

The study design, characteristics of participants, and the main results of the CANVAS Program have previously been published.<sup>6,9–11</sup> In brief, the CANVAS Program, comprising 2 similarly designed and conducted trials—CANVAS and CANVAS-R

(CANVAS-Renal)—was designed to assess the cardiovascular and renal safety and efficacy of canagliflozin, and how any potential benefits might balance against risks. There were 667 centers in 30 countries in the 2 trials that were scheduled for joint close-out and analysis when at least 688 cardiovascular events and a minimum of 78 weeks follow-up had been accrued for the last randomized participant, which occurred in February 2017.

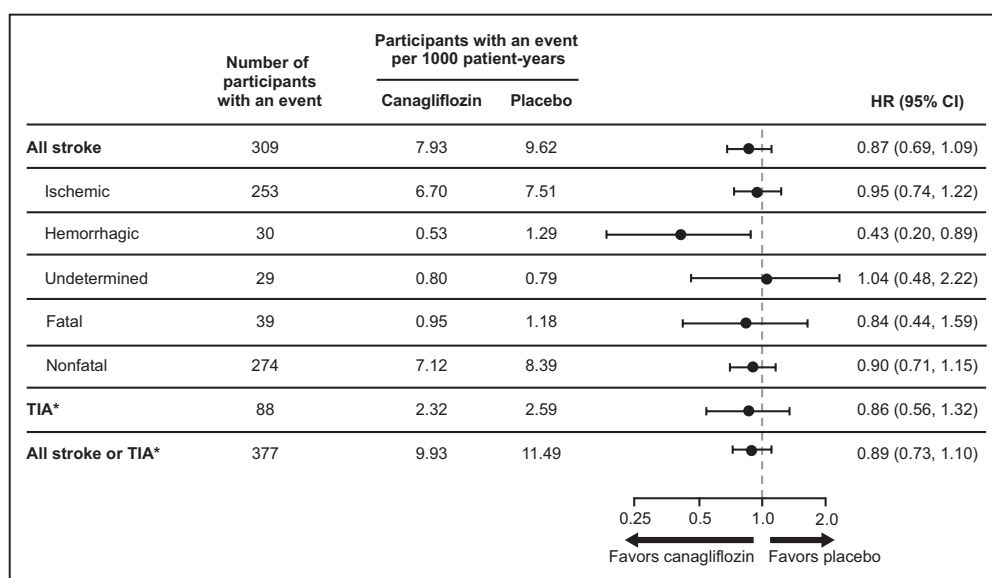
Data from the CANVAS Program will be made available in the public domain via the Yale University Open Data Access Project (YODA; <http://yoda.yale.edu/>) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months. The trial protocols and statistical analysis plans were published along with the primary CANVAS Program manuscript.<sup>6</sup>

### Participants

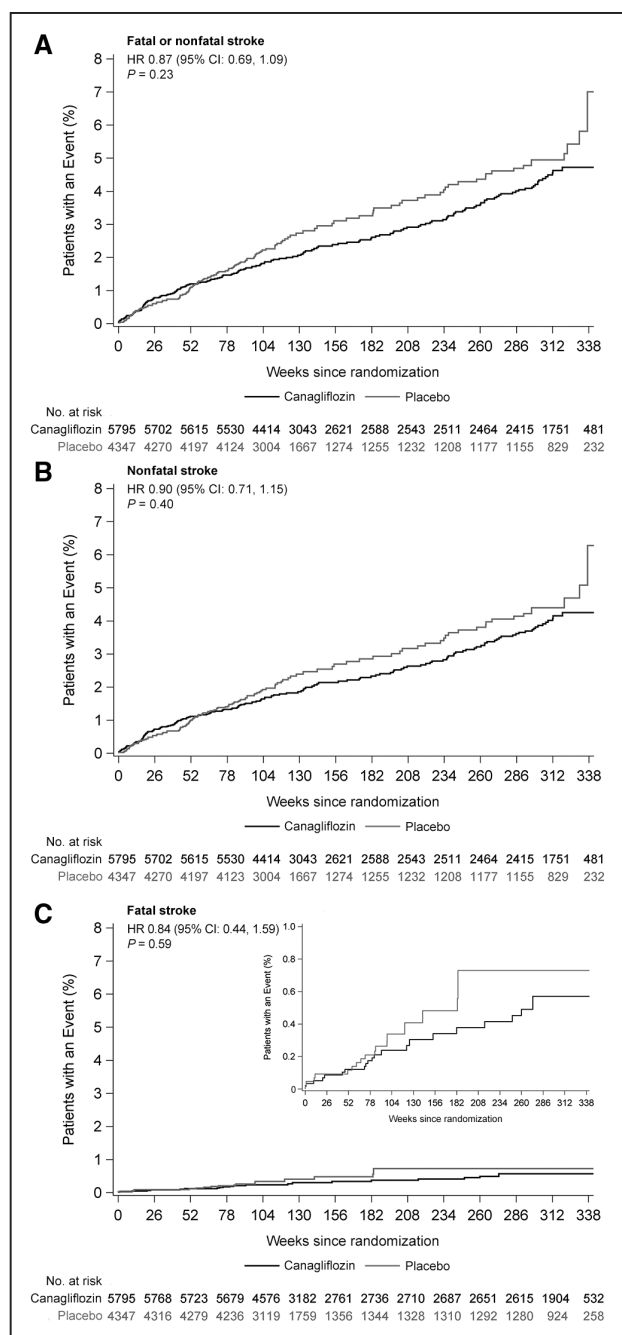
Participants in the CANVAS Program were those with type 2 diabetes mellitus (glycated hemoglobin [HbA1c]  $\geq 7.0\%$  and  $\leq 10.5\%$ ), aged  $\geq 30$  years with a history of symptomatic atherosclerotic cardiovascular disease, or  $\geq 50$  years with  $\geq 2$  risk factors for cardiovascular disease (duration of diabetes mellitus  $\geq 10$  years, systolic blood pressure [BP]  $> 140$  mmHg while on one or more antihypertensive agents, current smoker, microalbuminuria or macroalbuminuria, or high-density lipoprotein-cholesterol [HDL-C]  $< 1$  mmol/L). Patients treated with insulin and those with mild to moderate renal failure (estimated glomerular filtration rate [eGFR]  $\geq 30$  mL/min per  $1.73$  m<sup>2</sup>) were included. For the analyses presented in this report, a baseline diagnosis of cerebrovascular disease was based on a self-report of prior stroke or TIA.

### Randomization, Treatment, and Follow-Up

After a 2-week, single-blind, placebo run-in period, participants were randomized centrally through an interactive web response system using a computer-generated randomization schedule prepared by the study sponsor using randomly permuted blocks. Participants in CANVAS were assigned in a 1:1:1 ratio to canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, and participants in CANVAS-R were randomly assigned in a 1:1 ratio to canagliflozin or matching placebo, administered at an initial dose of 100 mg daily with optional up titration to 300 mg from week 13. Participants and all study staff were masked to individual treatment allocations until



**Figure 1.** Effects of canagliflozin on stroke and TIA. \*TIA was not adjudicated but based upon adverse event reports made by site investigators. Incomplete ascertainment of TIAs is possible because adverse event reporting in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program was streamlined from January 2014 to capture only serious adverse events and adverse events leading to discontinuation, and TIA events considered by the site investigator as nonserious would not be captured after this time. HR indicates hazard ratio; and TIA, transient ischemic attack.



**Figure 2.** Effects of canagliflozin on fatal and nonfatal stroke. **A**, Fatal or nonfatal stroke. **B**, Nonfatal stroke. Reprinted from Neal et al<sup>6</sup> with permission. Copyright ©2017, Massachusetts Medical Society. **C**, Fatal stroke. HR indicates hazard ratio.

the completion of the study. Use of other background therapy for glycemic management, prevention of stroke and other cardiovascular outcomes, and other diseases was according to best practice instituted in line with local guidelines.

Participants were followed after randomization in a face-to-face follow-up that was scheduled for 3 visits in the first year and at 6-month intervals thereafter, with alternating telephone follow-up between face-to-face assessments. Every follow-up included inquiry about primary and secondary outcome events and serious adverse events. Serum creatinine measurement with eGFR was performed at least every 26 weeks in both trials. Participants who prematurely discontinued study treatment continued scheduled follow-up wherever possible, with extensive efforts made to obtain full outcome data for

all during the final follow-up window that spanned from November 2016 to February 2017.

## Outcomes

The main outcome of interest for this report is fatal or nonfatal stroke. These were originally part of the primary composite outcome of major adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death) used for the CANVAS Program.<sup>6</sup> Additional exploratory outcomes for this report were fatal stroke; nonfatal stroke; ischemic stroke, hemorrhagic stroke, and stroke of undetermined type; TIA; stroke or TIA; major adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death); fatal or nonfatal myocardial infarction; hospitalized heart failure; cardiovascular death; all-cause mortality; progression of albuminuria (defined as >30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria); and serious decline in kidney function (defined as a 40% reduction in eGFR sustained for at least 2 consecutive measures, end-stage kidney disease, or death from renal causes). Possible intermediate markers of stroke risk were also analyzed, which included systolic BP, diastolic BP, body weight, HbA1c, cholesterol, triglycerides, hematocrit, urinary albumin-to-creatinine ratio, eGFR, and adverse events of atrial fibrillation reported during follow-up.

Endpoint Adjudication Committees (online-only Data Supplement) adjudicated all cardiovascular outcomes, renal outcomes, and deaths, with stroke events adjudicated by experienced stroke physicians (online-only Data Supplement). Stroke was defined using the 2013 American Heart Association/American Stroke Association criteria.<sup>12</sup> Ischemic and hemorrhagic stroke were determined by the neuroimaging findings, while undetermined stroke represented a clinical stroke without acute imaging to confirm the cause. TIAs were defined as a transient impairment of neurological function lasting <24 hours and without evidence of stroke on any acute neuroimaging. The Endpoint Adjudication Committee reviewed all suspected strokes and transient neurological events (including TIAs) as originally reported by the site investigators to determine whether the event met the criteria for a stroke. A reported TIA event could be adjudicated as a stroke event and it was removed from the analysis of TIA events if this was the case. Therefore, TIA events included in the analyses within this report were those not adjudicated to be stroke events.

## Statistical Analysis

Categorical variables were summarized as the number of patients (with corresponding percentages), and continuous variables were summarized as the mean and SD or the median and interquartile range. Differences in baseline characteristics between participants with a history of cerebrovascular disease compared with participants with no history of cerebrovascular disease were evaluated using generalized Cochran-Mantel-Haenszel test, ANOVA, or the Wilcoxon rank-sum test. Efficacy analyses were based upon the full, integrated dataset and the intent-to-treat approach, with the comparison being between all participants assigned to canagliflozin (regardless of dose) and all participants assigned to placebo. Analyses were based on the occurrence of the first event under investigation. The trial was powered to detect an effect on the primary composite outcome and not for the analyses of stroke. Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox regression models, with treatment as the exploratory variable, and factors of trial and history of cardiovascular disease included in the model. We tested the homogeneity of treatment effects across the 2 contributing trials using *P* values for interactions, and the same approach was used for testing comparability of effects across subgroups defined by baseline participant characteristics. Sensitivity analyses of fatal or nonfatal stroke were performed according to whether the events occurred on-treatment or within 7, 30, or 90 days of treatment discontinuation. Effects of canagliflozin on continuous intermediate markers of stroke risk were analyzed using an ANCOVA model with treatment

**Table 1. Effects of Canagliflozin on Possible Intermediate Markers of Stroke Risk**

|                                      | Change From Baseline to the Last Measurement* |              | Mean Treatment Difference (95% CI)† | P Value |
|--------------------------------------|---|--------------|-------------------------------------|---------|
|                                      | Canagliflozin                                 | Placebo      |                                     |         |
| Systolic BP, mmHg                    | −4.86 (0.19)                                  | −1.73 (0.22) | −3.14 (−3.71, −2.57)                | <0.001  |
| Diastolic BP, mmHg                   | −3.21 (0.11)                                  | −2.39 (0.13) | −0.82 (−1.15, −0.48)                | <0.001  |
| Body weight, kg                      | −3.21 (0.08)                                  | −0.81 (0.09) | −2.40 (−2.64, −2.17)                | <0.001  |
| HbA1c, %                             | −0.42 (0.02)                                  | −0.03 (0.02) | −0.39 (−0.44, −0.34)                | <0.001  |
| HDL-C, mmol/L                        | 0.04 (0.00)                                   | −0.01 (0.00) | 0.05 (0.04, 0.06)                   | <0.001  |
| LDL-C, mmol/L                        | 0.08 (0.01)                                   | −0.03 (0.01) | 0.12 (0.08, 0.15)                   | <0.001  |
| Ratio of LDL-C to HDL-C, %           | 0.32 (1.09)                                   | −0.70 (1.31) | 1.02 (−2.33, 4.36)                  | 0.55    |
| Triglycerides, mmol/L                | 0.08 (0.02)                                   | 0.02 (0.02)  | 0.06 (0.00, 0.11)                   | 0.04    |
| Total cholesterol, mmol/L            | 0.14 (0.01)                                   | −0.04 (0.02) | 0.18 (0.14, 0.22)                   | <0.001  |
| Hematocrit, %                        | 1.63 (0.05)                                   | −0.90 (0.06) | 2.53 (2.38, 2.68)                   | <0.001  |
| Albumin:creatinine ratio, mg/g       | 21.01 (6.30)                                  | 84.55 (7.49) | −63.55 (−82.73, −44.36)             | <0.001  |
| eGFR, mL/min per 1.73 m <sup>2</sup> | −1.82 (0.19)                                  | −3.87 (0.23) | 2.05 (1.47, 2.62)                   | <0.001  |

BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; and LDL-C, low-density lipoprotein-cholesterol.

\*Change from baseline to the last measurement was analyzed for participants with both baseline and at least 1 post-baseline measurement using an ANCOVA model with treatment as an independent effect and adjusting for trial and baseline value. Data are the change of least squares means (SE).

†The mean treatment difference of canagliflozin compared with placebo in the least squares means and associated 95% CIs were estimated from the model.

as an independent effect and adjusting for trial and baseline value. Change in the continuous intermediate marker from baseline to the last measurement throughout the trials and the difference of canagliflozin compared with placebo in the least squares means were estimated from the model. For atrial fibrillation, the HR with 95% CI was estimated from the same Cox regression model that was used to determine effects on stroke. Analyses were performed using SAS Enterprise Guide version 7.1.

### Standard Protocol Approvals, Registrations, and Patient Consents

The protocols for the 2 trials were approved by the ethics committees at each site. All participants provided written informed consent.

### Results

There were 10 142 patients in the CANVAS Program (Figure I in the [online-only Data Supplement](#)), and the mean follow-up time was 188.2 weeks. Mean age was 63.3 years, 35.8% were

women, mean duration of diabetes mellitus was 13.5 years, and 65.6% had a history of cardiovascular disease. A total of 1958 (19.3%) participants reported a history of cerebrovascular disease (stroke or TIA) at baseline. These participants were significantly different from other trial participants in most aspects of demography, disease history, and medication for the management of stroke risks, though the absolute magnitude of the differences was mostly small (Table I in the [online-only Data Supplement](#)). Atrial fibrillation was reported at baseline in 8.6% of those with cerebrovascular disease compared with 5.4% among those without.

### Effects of Canagliflozin on Stroke, TIA, and Stroke Subtypes

There were 309 trial participants with a fatal or nonfatal stroke recorded during follow-up (123 had prior stroke or TIA at baseline and 186 did not), at a rate of 7.93/1000 patient-years

**Table 2. Effects of Canagliflozin on Atrial Fibrillation**

|                     | Canagliflozin |   | Placebo   |   | HR* (95% CI)      | P Interaction |
|---------------------|---------------|---|-----------|---|-------------------|---------------|
|                     | Events, n     | Participants With an Event per 1000 pt-yr | Events, n | Participants With an Event per 1000 pt-yr |                   |               |
| Reported AF†        | 125           | 5.64                                      | 84        | 6.08                                      | 0.84 (0.64, 1.12) | 0.99          |
| Without AF history‡ | 100           | 4.75                                      | 67        | 5.11                                      | 0.82 (0.60, 1.11) |               |
| With AF history§    | 25            | 21.90                                     | 17        | 23.37                                     | 0.93 (0.50, 1.74) |               |

AF indicates atrial fibrillation; HR, hazard ratio; and pt-yr, patient-years.

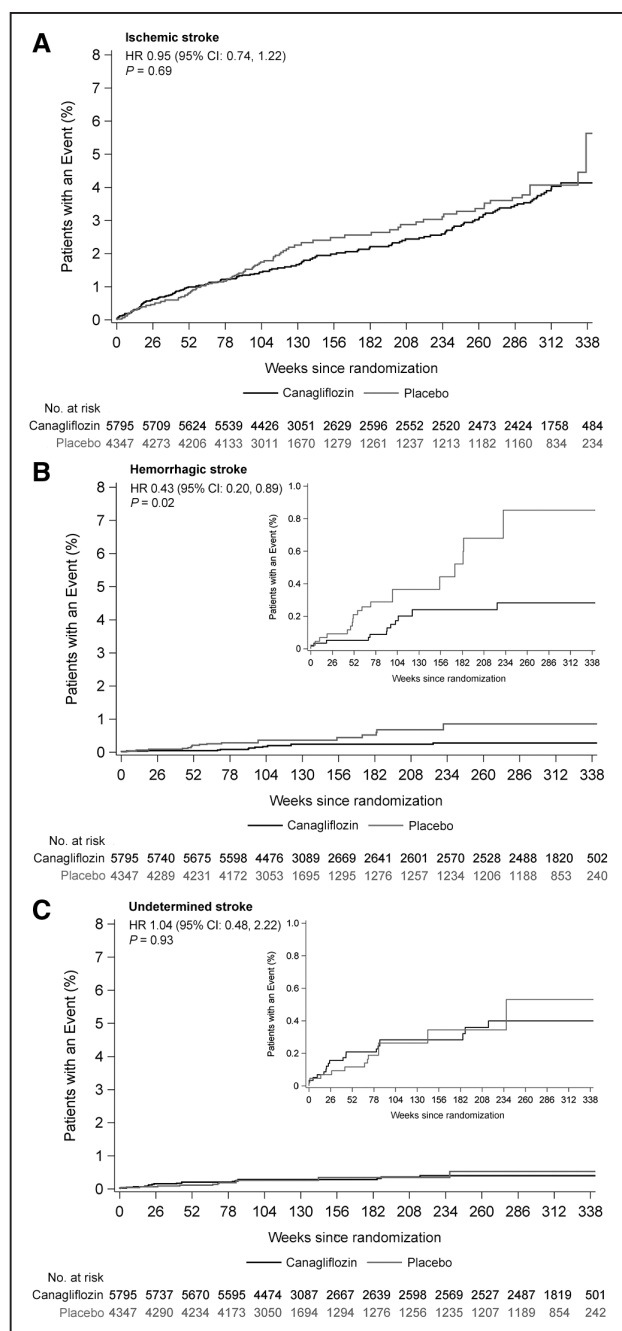
\*HRs and 95% CIs are determined from Cox regression models, with treatment as the exploratory variable and stratification according to trial and history of cardiovascular disease.

†AF events were identified from site investigator–reported adverse events.

‡AF events occurred during follow-up in participants without AF history.

§AF events occurred during follow-up in participants with AF history.





**Figure 3.** Effects of canagliflozin on stroke subtypes. **A**, Ischemic stroke. **B**, Hemorrhagic stroke. **C**, Undetermined stroke. HR indicates hazard ratio.

among those assigned canagliflozin and 9.62/1000 patient-years among those assigned placebo (HR, 0.87; 95% CI, 0.69–1.09; Figures 1 and 2). Hemorrhagic stroke was uncommon (30 events), with an observed reduction in risk for those allocated to canagliflozin compared with placebo (HR, 0.43; 95% CI, 0.20–0.89; Figures 1 and 3). The rate of ischemic stroke was also lower among those treated with canagliflozin compared with placebo ( $n=253$ ; HR, 0.95; 95% CI, 0.74–1.22), but this did not reach statistical significance. The rate of undetermined stroke events ( $n=29$ ) was similar in both groups (HR, 1.04; 95% CI, 0.48–2.22). Point estimates of effect were consistent and below unity for fatal stroke ( $n=39$ ; HR, 0.84;

95% CI, 0.44–1.59), nonfatal stroke ( $n=274$ ; HR, 0.90; 95% CI, 0.71–1.15), TIA ( $n=88$ ; HR, 0.86; 95% CI, 0.56–1.32), and the composite of stroke or TIA ( $n=377$ ; HR, 0.89; 95% CI, 0.73–1.10), but none of these individual results were statistically significant. The estimate of effect of canagliflozin on stroke risk did not vary with the time since the last dose of randomized treatment (Figure II in the [online-only Data Supplement](#)). The use of antithrombotic agents at baseline had no effect on the risk of hemorrhagic stroke (HR, 0.63; 95% CI, 0.22–1.76).

### Effects on Possible Intermediate Markers of Stroke Risk

There were favorable effects of canagliflozin compared with placebo on systolic BP, diastolic BP, body weight, HbA1c, HDL-C, urinary albumin-to-creatinine ratio, and eGFR. Small increases were observed for hematocrit, low-density lipoprotein-cholesterol (LDL-C), total cholesterol, and triglycerides with null effects on the ratio of HDL-C to LDL-C (Table 1). There was no detectable effect of canagliflozin compared with placebo on atrial fibrillation (HR, 0.84; 95% CI, 0.64–1.12), which was also true for the subsets of participants with and without atrial fibrillation history at baseline ( $P$  interaction=0.99; Table 2).

### Effects of Canagliflozin on Stroke in Patient Subgroups

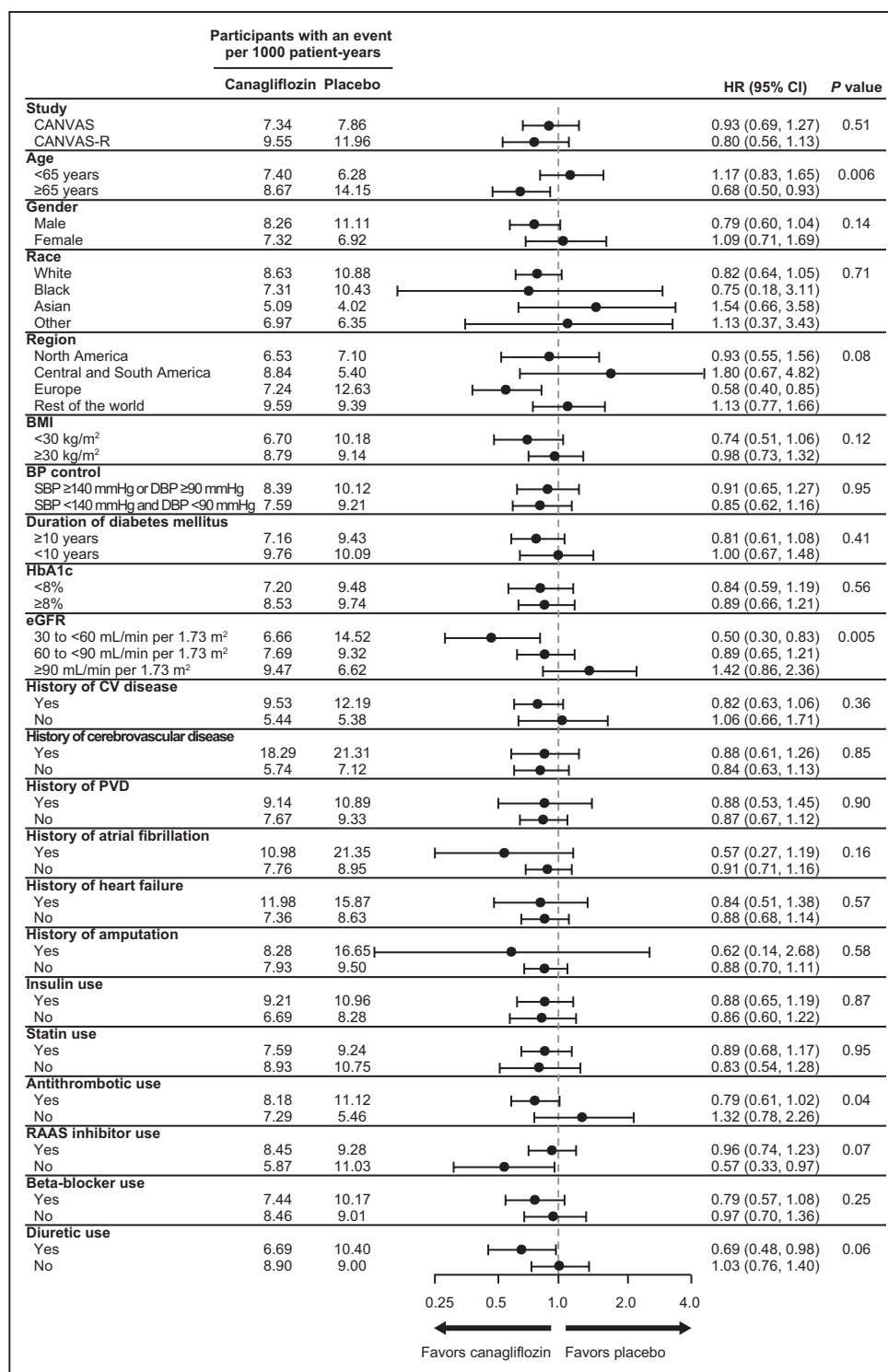
Effects of treatment on stroke were similar in CANVAS and CANVAS-R (HR, 0.93; 95% CI, 0.69–1.27 versus HR, 0.80; 95% CI, 0.56–1.13;  $P$  interaction=0.51) and for most other participant subgroups (Figure 4). The exceptions were subsets defined by age ( $P$  interaction=0.006), eGFR ( $P$  interaction=0.005), and use of antithrombotic therapy ( $P$  interaction=0.04), which indicated greater protection in older patients, those with lower eGFR, and those reporting antithrombotic use.

### Effects of Canagliflozin on Cardiovascular, Kidney, and Death Outcomes in Patients With and Without Cerebrovascular Disease at Baseline

Patients with stroke or TIA at baseline were at higher absolute risk of subsequent stroke and all other vascular outcomes, with 123 stroke events occurring in those 1958 patients with prior stroke or TIA versus 186 in the 8184 patients without. The proportional effects of canagliflozin compared with placebo were comparable in patients with and without cerebrovascular disease at baseline for cardiovascular, kidney, and death outcomes (all  $P$  interaction  $>0.19$ ; Figure 5).

### Discussion

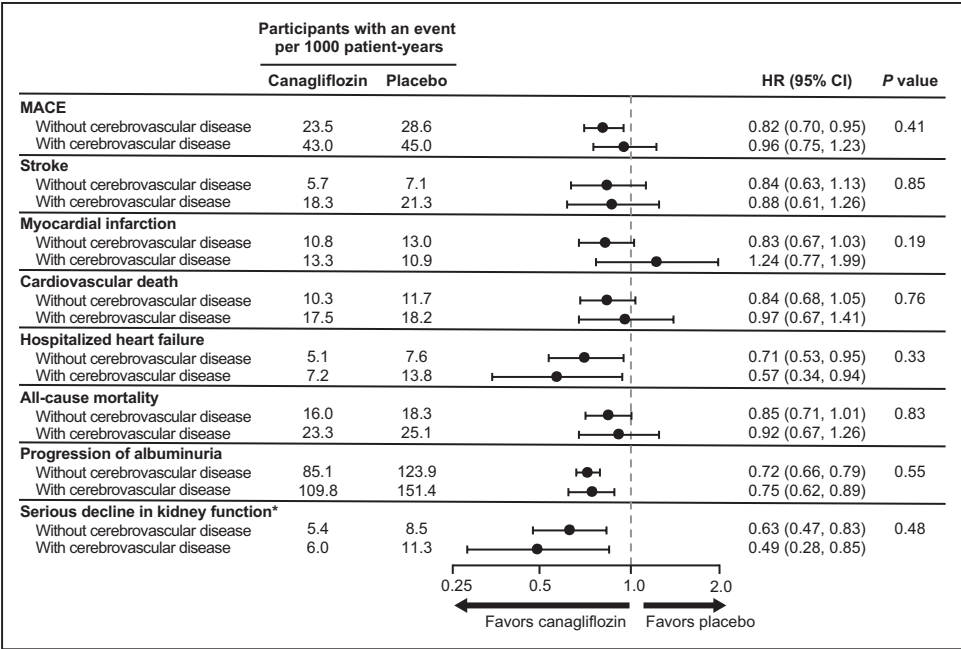
In the CANVAS Program, the composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death was significantly reduced, with a favorable (but not statistically significant) reduction in each of the 3 components.<sup>6</sup> Similarly, in these analyses, our primary outcome of stroke (fatal or nonfatal), although with a favorable point estimate of effect, was not statistically significant. The CANVAS Program was not powered to examine the individual contributions of stroke,



**Figure 4.** Effects of canagliflozin on stroke in patient subgroups. BMI indicates body mass index; BP, blood pressure; CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, CANVAS-Renal; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PVD, peripheral vascular disease; RAAS, renin-angiotensin-aldosterone system; and SBP, systolic BP.

myocardial infarction, and cardiovascular death to the primary outcome, but the observed effect on stroke events is consistent with that initially anticipated on the basis of the known BP-lowering effect of the compound.<sup>13</sup> Analysis according to pathological stroke subtype identified separately statistically significant protection against hemorrhagic stroke, albeit with

small numbers, though there was no clear effect on ischemic stroke or undetermined stroke. The hemorrhagic stroke result, if confirmed, could be consistent with a BP-lowering mechanism of stroke prevention with canagliflozin, at least in part, as hemorrhagic stroke is more strongly determined by higher BP than ischemic stroke.<sup>13</sup>



**Figure 5.** Effects of canagliflozin on cardiovascular and renal outcomes in patient with and without cerebrovascular (stroke or TIA) disease at baseline. eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death); and TIA, transient ischemic attack. \*Composite of 40% reduction in eGFR sustained for at least 2 consecutive measures, end-stage kidney disease, or death from renal causes.

Stroke, in particular, but also most other cardiovascular outcomes and death, occurred more frequently in patients with a baseline history of stroke or TIA compared with those without, though both sets of participants experienced comparable proportional reductions in the risks of these outcomes with use of canagliflozin.<sup>14</sup>

The effects of canagliflozin were broadly similar across a wide range of other participants, such as those using established treatments for the prevention of stroke, such as BP-lowering therapy, and patients of different ethnic backgrounds. The borderline significant interaction of canagliflozin treatment and stroke prevention with baseline use of an antithrombotic is likely to reflect a chance finding consequent upon the many comparisons made rather than a real effect. There was no corresponding evidence of an interaction by use of acetylsalicylic acid or anticoagulant therapy for stroke in EMPA-REG OUTCOME, though those participants all had a baseline history of cardiovascular disease and baseline use of these agents was greater.<sup>7</sup> By contrast, the significance level of the interactions of canagliflozin and stroke with age and eGFR make chance a less likely explanation, though the strong correlation between age and lower eGFR mean that these observations may not be independent of one another. A biological explanation for a greater effect of canagliflozin on stroke reduction in older compared with younger individuals or among individuals with impaired compared with preserved renal function is unknown, though comparable trends were noted in EMPA-REG OUTCOME.<sup>7</sup> The CREDENCE trial (Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation), which was done in patients with impaired renal function, will provide significant additional insight into these effects and may provide an indication of mechanism.<sup>15</sup>

Beneficial effects of canagliflozin on stroke might be anticipated based upon the BP lowering achieved with SGLT2 inhibition, since BP reduction is well known to significantly reduce both first and recurrent stroke, with greater reduction for hemorrhagic stroke.<sup>16–20</sup> Theoretical risks of hypoperfusion attributable to hypovolemia or hypotension<sup>21</sup> have not been observed in prior large trials of stroke prevention, and there was no evidence for such effects in the CANVAS Program. Hemorrhagic stroke is especially BP dependent,<sup>13</sup> so while the positive effect on this outcome observed in the CANVAS Program was based on relatively few events, a positive finding for hemorrhagic stroke is consistent with stroke epidemiology and clinical trials, albeit larger in magnitude than might have been expected for the observed BP reduction. Potential mechanisms for BP lowering with SGLT2 inhibition include natriuresis, osmotic diuresis (leading to volume depletion), and reduction in body weight.<sup>22</sup> The changes in lipid parameters with canagliflozin would tend to favor hemorrhagic stroke prevention, though effects on cholesterol were small. Additional anti-atherosclerotic effects of SGLT2 inhibition mediated through effects on glucose and obesity may also contribute to protection against stroke in the longer term.<sup>23</sup> There was no evidence of an adverse effect mediated through hemoconcentration, with favorable directions of effect for strokes of ischemic as well as hemorrhagic origin. Likewise, there was no evidence of any adverse effect of withdrawal of randomized treatment on stroke risk,<sup>7</sup> with constant HRs observed for strokes occurring on-treatment and at various intervals after treatment discontinuation.

The findings reported here are strengthened by the rigorous design and conduct of the trial, the prespecification of stroke as an outcome of interest, and the careful adjudication



of all potential stroke events according to recognized subtypes by an expert committee. This included screening all events reported as TIA for possible stroke events by the Endpoint Adjudication Committee, which resulted in additional stroke events being identified. Our study has limitations, the chief one being that the study was not powered to detect significant differences in total stroke events. The possible difference in effects by subtype of stroke needs to be interpreted with caution as a consequence but warrants further investigation. A further weakness is that TIAs were not themselves adjudicated, but all TIA events were screened by the stroke adjudicators to ensure stroke had not been misreported as TIA. Incomplete ascertainment of TIAs is possible because adverse event reporting in the CANVAS Program was streamlined from January 2014 to capture only serious adverse events and adverse events leading to discontinuation, and TIA events considered by the site investigator as nonserious would not be captured after this time. Missing TIA events should, however, be distributed nondifferentially between active and control groups and should not bias our results.

The unfavorable direction of effect reported for stroke in the EMPA-REG OUTCOME trial was not observed within the CANVAS Program, with a nonsignificant lower rate of all stroke events in those treated with canagliflozin and an indication of a possible beneficial effect for hemorrhagic stroke. The EMPA-REG OUTCOME trial recorded only about half as many hemorrhagic strokes as the CANVAS Program and did not report the effect of empagliflozin on that outcome, so comparability of the effects of the compounds on hemorrhagic stroke cannot be determined. Additional data from ongoing trials of SGLT2 inhibitors will provide further insight, and the CREDENCE trial, in particular, should clarify whether the effects of SGLT2 inhibition on stroke are enhanced in patients with chronic kidney disease.

## Conclusions

The CANVAS Program demonstrated a reduction in the primary composite outcome of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. There were too few events to separately define the effects of canagliflozin on stroke, but these analyses show that benefit is more likely than harm. The observed possible protective effect for hemorrhagic stroke was based on small numbers but warrants further investigation.

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